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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/997,464 | 12/23/1997 | DAVID STERN | 54202/JPW/SB | 1340 |

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| EXAMINER |
|---|
| ANGELL, JON E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 25 |

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Advisory Action | Application N . | Applicant(s) | |
|---|---|---|---|
| | 08/997,464 | STERN ET AL. | |
| | Examiner | Art Unit | |
| | J. Eric Angell | 1635 | |

*--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

THE REPLY FILED 04 December 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *04 December 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): *See Continuation Sheet*.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1,3,4 and 34-37*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)( PTO-1449) Paper No(s). _____.

10.☐ Other: _____

J. Eric Angell

Continuation of 3. Applicant's reply has overcome the following rejection(s): because claims 11 and 12 have been cancelled, the rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph is now moot.

Continuation of 5. does NOT place the application in condition for allowance.

Claims 11 and 12 have been cancelled thus rendering the rejection of claims 11 and 12 moot.

It is noted that claim 5 was cancelled in the communication filed 3/11/02 (as Paper No. 20). Therefore, Claims 1, 3, 4 and 34-37 are pending in the application (not claims 1, 3-5 and 34-37).

Claims 1, 3, 4, and 34-37 stand rejected under 35 U.S.C. 103(a) for the reasons set forth in a previous Office Action. Applicants request reconsideration of the rejection of claims 1, 3, 4, and 34-37 for the following reasons.

First Applicants note that the Examiner conceded that neither Wolozin or Yan indicate that an interaction between RAGE and PS2 existed. Applicants contend that absent the data provided in the applicants disclosure, it would not have been predictable that such an interaction would be useful for identifying neuroprotective therapeutics in a cell (see p.6-8 of Applicant's response). In response, it is noted that although neither Wolozin or Yan teach a direct interaction between RAGE and PS2, it was indicated in the previous Action that it would have been obvious to one of skill in the art that there is at least an indirect interaction between RAGE and PS2 via amyloid-beta, as evidenced by the fact tthat amyloid-beta increases apoptosis in cells expressing either RAGE or mutant PS2. Therefore, given the fact that 1) Yan teaches that amyloid-beta-RAGE interaction induces apoptosis which contributes to neurotoxicity and dementia by activating oxidant stress and cellular activation (cytokine production, chemotaxis and haptotaxis); and 2) Wolozin teaches that amyloid-beta increases apoptosis in cells expressing mutant PS2 (as well as wild-type PS2) which leads to apoptotic neuronal cell death; it would have been predictable that a method comprising adminstering amyloid-beta to a cell expressing both RAGE and a mutant presenilin-2 protein could be useful for identifying neuroprotective therapeutics as well as methods for identifying compounds which inhbit neurocytotoxicity as well as compounds which inhibit the cytotoxic effects of cytokines and oxidative stress on neuronal cells. Furthermore, even without the teaching of a direct interaction between RAGE and PS2, it would have been predictable that a cell expressing both RAGE and mutant PS2, could be used to identify neuroprotective therapeutics because it was known in the art that both RAGE and mutant PS2 were involved in neurodegeneration (as evidenced by Wolozin and Yan).

Second, Applicants contend that there is an unexpected interaction between RAGE and PS2 which results in a synergistic increase in apoptosis in cells expressing RAGE and PS2. In response, as mentioned in the previous Office Action, the Examiner respectfully disagrees with the applicants contention that there is a synergistic interaction between RAGE and PS2 which results in a dramatic increase in apoptosis for the following reasons: First, although the applicants contend a synergistic interaction between mutant PS2 and RAGE, no data in the specification support such a notion. The specification discloses apoptotic levels in amyloid-beta treated control cells (i.e. mock-transfected cells), cells that express RAGE and cells that express RAGE and mutant PS2 (see Figure 3 of the instant application). Figure 3 does not show a control wherein the treated cells express mutant PS2 but not RAGE. Without a comparison of cells expressing mutant PS2 alone versus cells expressing both mutant PS2 and RAGE, a synergistic interaction cannot be determined. Therefore, it cannot be determined if the cells expressing both mutant PS2 and RAGE show an increase in apoptosis compared to cells expressing mutant PS2 but not RAGE.

It is acknowledged that the specification discloses "while mutant presenilin-2 by itself has little effect on apoptosis, cells co-transfected to express mutant presenilin-2 and RAGE showed a dramatic increase in apoptosis..." However, Wolozin appears to contradict this statement. Specifically, Wolozin teaches, "cells transfected with vector (CTRL) or wild type human PS2 (PS2wt) show low levels of apoptosis, whereas cells transfected with N141I mutant human PS2 (PS2mut) in which Asn is mutated at position 141 [the same mutant PS2 used by the Applicants], show elevated levels of apoptosis and more cell detachment (see legend for Figure 1C, p. 1710). It is also clear in Figure 1D of Wolozin that aproximately 60% of cells expressing mutant PS2 show apoptosis, which appears to contradict the assertation that mutant PS2 itself has little effect on apoptosis.

Considering the lack of a working example clearly indicating a syngerstic interaction between RAGE and mutant PS2 and further considering the fact that the prior art indicates that mutant PS2 can have a dramatic effect on increasing apoptosis by itself (rather than a "little effect on apoptosis" as asserted in the specification), it cannot be concluded that there is synergistic interaction bewtween RAGE and mutant PS2. Without evidence of an unexpected result (for instance, by Declaration), the rejection of claims 1, 3, 4 and 34-37 over Wolozin in view of Yan stands.

DAVE T. NGUYEN
PRIMARY EXAMINER